EXHIBIT A

Docket No.: 069738-0011 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Kaiser, Jon D.	Customer No.: 41552
Appl. No.	:	10/750,545	Confirmation No.: 5578
Filed	:	December 31, 2003	
Title	:	NUTRIENT COMPOSITIONS AND METHODS FOR ENHANCED EFFECTIVENESS OF THE IMMUNE SYSTEM	
Grp./A.U.	:	1616	
Examiner:	:	Ernst V. ARNOLD	

DECLARATION UNDER 35 U.S.C. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jon D. Kaiser, declare as follows:

1) I am a practicing physician and currently a member of the clinical teaching faculty at UCSF Medical School in the Department of Medicine and the Medical Director of Integrative Health Consulting, Inc. I also practice medicine privately where my specialty is in Human Immunodeficiency Virus (HIV) and the diseases of the immune system. I previously practiced internal and emergency medicine at Valley Emergency Physicians, Kaiser General Medicine Outpatient Clinic and Novato Family Practice Center.

2) I obtained a Bachelor of Arts, majoring in Philosophy with a specialization in biochemistry, in 1980 from the State University of New York at Binghamton, and my M.D. from the University of Texas Medical School at Houston in 1984. I completed my residency at the Kaiser Foundation Hospital, San Francisco, California, in internal medicine. I have authored or co-authored numerous papers as well as consulted for major pharmaceutical corporations in the fields of Human Immunodeficiency Virus (HIV), Acquired Immune Deficiency Syndrome

(AIDS) and diseases of the immune system. I also have appeared on CNN, KRON, News at Noon and French Public Television in relation to these expertise. My curriculum vitae is attached as Exhibit 1.

3) I have read the Office Action mailed May 16, 2007, for U.S. Application Serial No. 10/750,545, which issued following the personal interview with Examiners Arnold and Richter. Specifically, I understand that claims 1-27 have been rejected for being obvious over Kosbab, U.S. Patent Application 2001/0031744, because Table 3 lists dosage ranges of high potency antioxidants within highly saturable amounts and Table 4 provides a formulation containing coenzyme Q10, N-acetyl-L-cysteine and lipoic acid, albeit not in highly saturable amounts. The Examiner concludes that it would be obvious to one of ordinary skill to modify the components listed in Table 4 with the dosages in Table 3 to arrive at the claimed invention.

4) I also understand that claims 1-27 have been rejected for being obvious over Gorsek, U.S. Patent No. 6,103,756, in view of Ames et al., U.S. 5,916,912 and Kosbab, because it would have been obvious to modify the formulation of Gorsek, containing certain antioxidants but lacking acetyl L-carnitine, with a highly saturable amount of high potency antioxidants as purported to be suggested by Ames et al. and Kosbab for the purpose of reversing indicia of aging.

5) I further understand that claims 1-27 have been rejected for being obvious over Barker et al., WO 00/76492, in view of Ames et al. and Kosbab because it would have been obvious to add alpha lipoic acid, acetyl L-carnitine, co-enzyme Q10, glutathione, bioflavonoid complex vitamin B6, beta-carotene and zinc as purported to be described in Kosbab and Ames et al. to the formulation of Barker et al. because Kosbab and Ames et al. describe formulations containing these antioxidants and zinc.

6) The claimed nutrient composition containing at least one vitamin antioxidant, at least one mineral antioxidant and a highly saturable amount of at least three high potency antioxidants was discovered through my years of experience in the fields of HIV, AIDS and nutrient supplementation. To my knowledge, the claimed nutrient composition is the only formulation shown to enhance the immune systems of people with HIV infection, as measured by a significant increase in CD4 counts, currently taking antiviral treatment.

7) The claimed nutrient composition contains less than 2% of the ingredients variously listed in the Kosbab publication. In my view, after years of experience in treating people with HIV and AIDS and much effort to develop an optimal formulation that helps improve the lives of these patients, the claimed nutrient composition would not have been an obvious modification of any of the formulas of Kosbab alone, or the formulas of Gorsek or Barker et al. in view of Kosbab and Ames et al. or Ames et al. and Kosbab, respectively, because one of ordinary skill in the art would not have known where to begin or how to limit the large number of ingredients in Kosbab's various formulations to arrive at the claimed invention. Nor would one of ordinary skill in the art have known where to begin or would have had a reason to add the claimed five antioxidants in the claimed amounts – at least one vitamin antioxidant, at least one mineral antioxidant and three high potency antioxidants in highly saturable amounts – to arrive at the claimed invention.

8) As evidence that the claimed nutrient composition is not simply an obvious reorganization of ingredients described in the cited publications is the publication attached as Exhibit 2. A comparison of the results reported in Exhibit 2 with the results described in the application shows that the claimed nutrient composition produces unexpected and synergistic results with respect to augmenting immune strength.

9) One aspect of the claimed nutrient composition is combining at least three high potency antioxidants in a highly saturable amount. Exhibit 2 is a publication by McComsey et al. reporting the effects of antioxidant treatment on HIV-infected patients (McComsey et al., *JAIDS* 33:605-07 (2003)). McComsey et al. administered a formulation containing a single high potency antioxidant at 600 mg twice daily (*Id.*, p.606, col. 1, second para.) plus two antioxidant vitamins (vitamins C and E). Table 1 shows the change in baseline characteristics for a number of indicators in the study including $CD4^+$ cell count, which is the most relied on indicator of immune strength in HIV positive or AIDS patients. After 24 weeks of treatment, the $CD4^+$ cell count actually decreased about 4% from baseline compared to the control group.

10) In contrast, the results described in Example I of the Application show that after only 12 weeks of treatment with the claimed nutrient composition containing a highly saturable amount of three high potency antioxidants an average increase of 26% in $CD4^+$ cell counts was

observed compared to only 2% in the placebo control (Application, p. 43, Table 5). This level of increase provided a highly significant improvement in the $CD4^+$ cell count and is more than what would be expected if there was just an additive effect from each high potency antioxidant alone.

11) Further evidence that the invention is unobvious over any rearrangement of ingredients described in Kosbab, Ames et al. and/or Barker et al. is supported by the success the claimed nutrient composition has achieved in the patient care industry. The formulations of the claimed nutrient compositions exemplified in Figures 1 and 2 of the application are marketed as K-PAX Immune Support Formula. These formulations have gained approval by two New York State Health Care programs, The New York AIDS Drug Assistance Program (ADAP) and the New York State Medicaid Program, and are provided free of charge to patients diagnosed with HIV/AIDS. Direct payment to the pharmacy is made by the State of New York. Products covered by these two government programs must undergo a rigorous evaluation process by a panel of health care experts prior to their approval. The fact that two state agencies have deemed the claimed nutrient composition sufficiently beneficial to be eligible for coverage by state funded programs indicates that the K-PAX Immune Support Formula fulfills a need lacking in other nutrient formulations.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Date: 7/17/07 By: _____
Jon D. Kaiser, M.D.

SDO 70342-1.069738.0011

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Jon D. Kaiser, M.D.
Curriculum Vitae

Undergraduate State University of New York at Binghamton
- *Bachelor of Arts, Philosophy, 1980*
- *Specialization in Biochemistry, Phi Beta Kappa*

Graduate University of Texas Medical School at Houston
- *Doctor of Medicine, 1984*
- *Honors in Internal and Emergency Medicine*

Postgraduate Kaiser Foundation Hospital, San Francisco, CA
- *Internal Medicine Residency, 1984-1985*

Faculty UCSF Medical School, Department of Medicine
- *Clinical Teaching Faculty, 4/99 - Present*

Experience
- HIV Specialist, Private Practice – 1987 to Present
- Integrative Medicine Consultant, Private Practice – 1987 to Present
- Medical Director, Integrative Health Consulting, Inc.– 2001 to Present
- Medical Director, The Jon Kaiser Wellness Center- 9/97-1/00 SF, CA
- Medical Director, Conant Group Wellness Center- 7/95-8/97, SF, CA
- Novato Family Practice Center, Novato, CA 1987-1989
- Kaiser General Medicine Outpatient Clinic, SF, CA 1988-1989
- Valley Emergency Physicians, Oakland, CA 1985-1988

Specialty
- HIV Care/Diseases of the Immune System/ Integrative Medicine

Licensure

- California Medical License
- HIV Specialist 2002 – Present, American Academy of HIV Medicine

Organization Memberships

- International Journal of Infectious Diseases – Editorial Review Board, 2006-Present
- Ontario HIV Treatment Network – Scientific Review Committee, 2005-Present
- American Academy of HIV Medicine, Founding Board Member
- American Academy of HIV Medicine, Reimbursement Committee Chairman, March 2000- January 2002
- California Academy of HIV Medicine, Founding Board Member
- Community Consortium of HIV Physicians, 1989 – 2007
- American Medical Association - 2002-2004
- California Medical Association - 2002-2004
- Marin Medical Society - 2002-2004
- California Pacific Medical Center Staff, 1992-2002
- San Francisco Children's Hospital Staff Physician, 1989-1992
- Community Research Alliance/ Scientific Advisory Committee.
- Healing Alternatives Foundation/Advisory Committee
- Immune Enhancement Project/Scientific Advisory Committee

Industry Consulting

- Bristol-Myers Squibb Distinguished Faculty
- Gilead Sciences Distinguished Speakers Bureau
- Boehringer Ingelheim Physician Advisory Board
- Abbott Laboratories Physician Advisory Board
- Glaxo SmithKline Physician Advisory Board
- Agouron National Physician Advisory Panel
- Ortho Biotech HIV Specialist Speakers Bureau

Research Projects

- Micronutrient Supplementation – Double –Blind, Placebo-Controlled Investigation of Clinical and Immunological Effects – Principal Investigator, 2001-2005
- BioTech General Oxandrolone Research Study
- Agouron Nelfinavir Research Study
- 3TC Open Label Study Research Program

- ddI Open Label Study Research Program
- ddC Open Label Study Research Program
- D4T Expanded Access Research Program
- Abacavir Expanded Access Research Program
- Amprenavir Expanded Access Research Program
- Independent HIV Research: Preventing HIV Disease Progression, UCSF Assisted

Government Affairs

- NRCC Physician Advisory Board, Honorary Co-Chairman
    - Physician of the Year Award, California - 2003

Books and Publications

- ***Micronutrient Supplementation Increases CD4 Count in HIV-infected Individuals on Highly Active Antiretroviral Therapy: A Prospective, Double-Blinded, Placebo-Controlled Trial.*** Kaiser JK, Campa AM, Ondercin JP, et al. *JAIDS* 2006;42[5]: 523-528.
- ***Micronutrient Supplementation Increases CD4 Count in HIV-infected Individuals on Highly Active Antiretroviral Therapy: A Prospective, Double-Blinded, Placebo-Controlled Trial.*** Final results presented at the 2006 World AIDS Conference, Toronto, Canada, August 14th, 2006 [Abstract # MOAB0402].
- ***Broad-spectrum Micronutrient Supplementation in HIV-infected patients with Dideoxynucleoside-related Peripheral Neuropathy: A Prospective, Double Blind, Placebo Controlled Trial.*** Preliminary results presented at the 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 8-11, 2004 [Abstract #494].
- ***Comparison of Drug Susceptibility in HIV-1 from antiretroviral (ART) experienced subjects as assessed by the Antivirogram and Pheno-Sense assays,*** Presented at the 1st International AIDS Society Conference on HIV Pathogenesis and Treatment, Buenos Aires, Argentina (July 8-11, 2001).
- ***Genotypic and Phenotypic Characteristics of HIV-1 Isolates From Patients Failing d4T-Containing Regimens,*** Presented at the XIII International AIDS Conference, Durban, South Africa (July 9-14, 2000).
- ***Healing HIV- How To Rebuild Your Immune System,*** (HealthFirst Press January, 1999).
- ***Complementary Therapies in HIV,*** Alternative Therapies in Health and Medicine, (July, 1996).

- ***Immune Power The Comprehensive Healing Program for HIV,*** (St. Martin's Press July, 1993).

Television

- ***The Wellness Program*** Hosted monthly, prime time health-oriented cable television series exploring the frontiers of health and healing in the 90's, September '98 - March '99
- ***AIDS Update*** Appeared as a featured guest eight times on this award winning monthly cable television show.
- Dr. Kaiser has also **appeared on CNN, KRON, News at Noon, and French Public Television.**

Speaking Engagements

2006

- **Micronutrient Supplementation Increases CD4 Count in HIV-infected Individuals on Highly Active Antiretroviral Therapy: A Prospective, Double-Blinded, Placebo-Controlled Trial.** Presented at the World AIDS 2006, August 14, 2006, Toronto, Canada.

- **"Living a Normal & Healthy Lifespan with HIV"**
  - New York, NY – March 29, 2006
  - Palm Springs, CA – May 18, 2006
  - San Diego, CA – May 31, 2006
  - Manchester, United Kingdom – June 19, 2006
  - London, United Kingdom – June 20, 2006
  - London, United Kingdom – June 21, 2006
  - Birmingham, United Kingdom – June 22, 2006

2005

- **Micronutrient Therapy as Part of the Comprehensive Treatment of HIV – Keynote Speaker at the Ontario HIV Treatment Network** – Toronto, Canada - November 24, 2005

- **Micronutrient Therapy as Part of the Comprehensive Treatment of HIV – Callen-Lorde Medical Clinic Ground Rounds** – New York, New York – October 26, 2005

- **The Use of Micronutrients as Immunomodulators in the Treatment of HIV** - University of California San Francisco Medical Student AIDS Forum – San Francisco, California – October 8, 2005

- **"Living a Normal & Healthy Lifespan with HIV"**

San Jose, CA – April 7, 2005
Ft. Lauderdale, FL – April 14, 2005
San Luis Obispo, CA–April 23, '05
Bellmawr, NJ – April 26, 2005
Philadelphia, PA – April 27, 2005
Dallas, TX – April 28, 2005
Tuscon, AZ – May 19, 2005
Atlanta, GA – May 23, 2005
Chicago, IL – May 24, 2005
New York, NY – May 26, 2005
Seattle, WA – June 2, 2005
Austin, TX – September 26, 2005
NYC, NY – October 26, 2005
Charlotte, NC – October 27, 2005
Tampa Bay, FL – November 8, '05

2004

- Vitamins Hormones, and Treatment Interruptions (STI's): A Potpourri of HIV Treatment Pearls, **Portland**, Oregon, December 2004.
- How to Live a Normal Lifespan with HIV, **Portland**, Oregon, December 2004.
- An Integrative Medicine Approach to Treating HIV - **Palm Springs**, California, December 2004.
- An Integrative Medicine Approach to Treating HIV - **Houston**, Texas, November 2004.
- An Integrative Medicine Approach to Treating HIV - **San Diego**, California, November 2004.
- An Integrative Medicine Approach to Treating HIV - **Miami**, Florida, October 2004.
- An Integrative Medicine Approach to Treating HIV - **Pasadena**, California, October 2004.
- An Integrative Medicine Approach to Treating HIV -**Los Angeles**, California, September 2004.
- An Integrative Medicine Approach to Treating HIV - **San Francisco**, California, September 2004
- Results of the HIV Micronutrient Study - **New York**, New York, June 2004.
- HIV Treatment Update, **Los Angeles**, California, March 2004.
- HIV Treatment Update, **San Francisco**, California, March 2004.

2003

- Enhancing Treatment Outcomes / Preventing Drug Side Effects – San Francisco, CA November 2003, Attendance 150+
- Enhancing Treatment Outcomes / Preventing Drug Side Effects – Phoenix, AZ, September 2003, Attendance 50+
- Vitamins and Micronutrient Support in HIV Disease – a lecture to physicians and researchers, New York City, NY - March 2003, Attendance 75+
- Emerging Issues in HIV Care – Vitamins and Micronutrient Support in HIV Disease – a lecture to physicians, San Francisco, CA - June 2003, Attendance 60+
- Enhancing Treatment Outcomes / Preventing Drug Side Effects – Project HOPE, San Jose, CA May 2003, Attendance 100+

- Enhancing Treatment Outcomes / Preventing Drug Side Effects – San Francisco, CA March 2003, Attendance 150+
- Enhancing Treatment Outcomes / Preventing Drug Side Effects – New York City, NY March 2003, Attendance 75+
- Enhancing Treatment Outcomes / Preventing Drug Side Effects – Los Angeles, CA January 2003, Attendance 200+

2002

- An Integrative Approach to Treating HIV/AIDS – A Kaiser Foundation Health Plan Video Conference – Oakland, CA – November 2002, Attendance 500+
- Enhancing Treatment Outcomes / Preventing Drug Side Effects – San Francisco, CA October 2002, Attendance 150+
- Enhancing Treatment Outcomes / Preventing Drug Side Effects – NYC, NY September 2002, Attendance 150+
- Enhancing Treatment Outcomes / Preventing Drug Side Effects – Philadelphia, PA September 2002, Attendance 150+
- Complementary Treatments for HIV Disease - CA Department of Public Health, Office of Community Based Services – San Jose, CA – September 2002, Attendance 75+ HIV nurse practitioners and case managers
- The Prevention and Treatment of AIDS Wasting Syndrome – Oakland, CA – September 2002, Attendance 30+ Treatment Providers
- The Prevention and Treatment of AIDS Wasting Syndrome – Fresno, CA – August 2002, Attendance 30+ Treatment Providers
- HIV Update – Vacaville State Prison, Vacaville, CA- August 2002, Attendance 30+
- Marin AIDS Foundation - HIV Update: Enhancing Treatment Outcomes - Preventing Drug Side Effects – San Rafael, CA, June 2002, Attendance 75+
- Maui, HI, Maui AIDS Foundation Conference 2002, April 2002, Attendance 100+
- Nutrition and HIV Disease – Colusa, CA- April 2002, Attendance 30+

2001

- The Prevention of Antiviral Drug Side Effects – Eureka, CA, Humboldt County Dept. of Public Health AIDS Conference, October,12 2001, Attendance 100+
- The Prevention and Treatment of Mitochondrial Toxicity, Lipoatrophy, and Lipodystrophy – Phoenix, AZ, September,14. 2001, Attendance 100+
- Maui, HI, Maui AIDS Foundation Conference 2001, April 2001, Attendance 100+

2000

- The Prevention and Treatment of Mitochondrial Toxicity, Lipoatrophy, and Lipodystrophy – A 10 city lecture tour to physicians, Oct/Nov 2000
- Enhancing Antiviral Therapy / Minimizing Antiviral toxicities – A lecture to physicians, Sept. 2000
- Heterochat Poz Summit 2000 - Keynote Speaker, San Diego, CA, June 9 2000, Attendance 500+
- South Lake Tahoe, CA, "Healing HIV Health Fair Community Forum", June 2000, Attendance 100+

- North Lake Tahoe, CA, "Healing HIV Health Fair Community Forum", April, 2000, Attendance 100+
- Grass Valley, CA, "Healing HIV Health Fair Community Forum", April, 2000, Attendance 100+
- Kauai, HI, Kauai AIDS Foundation Conference 2000, April 2000, Attendance 60+
- Maui, HI, Maui AIDS Foundation Conference 2000, April 2000, Attendance 100+

1999

- "Healing HIV Health Fair Community Forums" : Miami, Los Angeles, New Orleans, Phoenix, San Diego, Washington D.C, Denver, Portland, San Francisco, New York City, **Total yearly attendance 4200+**
- Dallas, TX The prevention and treatment of HIV-related fatigue, Oct. 1999, Attendance 150+
- San Diego, CA The prevention and treatment of HIV-related fatigue, May 1999, Attendance 150+
- Maui, HI, Maui AIDS Foundation Conference 1999, May 1999, Attendance 200+
- Honolulu, HI Hawaii Pharmacists Convention "Combining alternative with standard medical therapies in HIV/AIDS treatment
- Cannes, France, April 1999, Abstract accepted for presentation at the Third International Conference on Nutrition and HIV Infection, "Elimination of malnutrition cofactors in combination with HAART therapy improves clinical outcomes".
- Princeton, NJ, Feb. 6, 1999, Keynote Speaker-The 1999 New Jersey Conference on HIV/AIDS, Attendance 250+

1998

- "Healing HIV Health Fair Community Forums" : Miami, Los Angeles, New Orleans, Phoenix, San Diego, Washington D.C, Denver, Portland, San Francisco, New York City, **Total yearly attendance 4200+**
- Tampa, FL, December 4, For AIDS Care Today, Inc., Keynote Speaker yearly fundraiser banquet, Attendance 400+
- Greenville, South Carolina, December 4, Medical Grand Rounds: HIV care in the 21st Century, Keynote Speaker, Attendance 150+
- Tampa, FL, December 1, St. Joseph's Hospital World AIDS Day Program, Keynote Speaker, Attendance 100+
- AIDS, Medicine, & Miracles, Dallas, TX, Featured speaker, Attendance 60+
- Illinois Dept. of Public Health, HIV and STD Update Conference, Attendance 150
- 1998 "Healing HIV Health Fair Community Forums" : Miami, Los Angeles, New Orleans, Phoenix, San Diego, Washington D.C, Denver, Portland, San Francisco, New York City, Total attendance 3500+

1997

- Los Angeles, CA, March 15, Nutrition and Preventing Weight Loss in HIV plus New Trends in Antiviral Therapy, Community Forum, Attendance 250+

- Miami FL, February 22, Nutrition and Preventing Weight Loss in HIV plus New Trends in Antiviral Therapy, Community Forum, Attendance 2oo+

1996

- Chicago, IL, November 16, Nutrition and Preventing Weight Loss in HIV plus New Trends in Antiviral Therapy, Community Forum, Attendance 3oo+
- New York City, NY, October 26, Nutrition and Preventing Weight Loss in HIV plus New Trends in Antiviral Therapy, Community Forum, Attendance 5oo+
- San Francisco, CA, September 21, Nutrition and Preventing Weight Loss in HIV plus New Trends in Antiviral Therapy, Community Forum, Attendance 6oo+
- New Orleans, LA, June 25, New Trends in Treatment of HIV - Fatigue, Protease Inhibitors, and Wasting Syndrome, Private dinner for physicians, sponsored by Ortho Biotech.
- San Francisco, CA, May 20, Nutrition and HIV, Conant Community Forum. Sausalito, CA, April 10, Trends in Alternative Therapies, New Dimensions Radio interview.
- New Orleans, LA, March 28, The Prevention and Elimination of Fatigue in HIV, Ortho Biotech Community Forum.

1995

- Miami, FL, December 9, The Prevention and Elimination of Wasting Syndrome, Community Forum.
- Houston, TX, November 18, The Prevention and Elimination of Wasting Syndrome, Community Forum.
- New York, NY, October 28, The Prevention and Elimination of Fatigue in HIV, Ortho Biotech Community Forum.
- Denver, CO, October 14, Update on Alternative Therapies in HIV, Project Angel Heart/Colorado Health Fair.
- Denver, CO, October 13, The Prevention and Elimination of Wasting Syndrome, Presentation to the physician community.
- Miami, FL, October 7, The Prevention and Elimination of Fatigue in HIV, Ortho Biotech Community Forum.
- San Diego, CA, September 23, Nutrition and HIV, HIV/AIDS in Women Conference.
- San Francisco, CA, July 18, Viacom Cable AIDS Update Series, Television appearance, guest speaker.
- Los Angeles, CA, July 8, The Prevention and Elimination of Fatigue in HIV, Ortho Biotech Community Forum.
- Washington, D.C., April 27, Complementary Therapies and HIV Presentation, National Institutes of Health Office of Alternative Medicine Conference.
- Portland, OR, April 14, A Comprehensive Healing Program for HIV, Project Quest Annual Retreat.
- San Francisco, CA, March 4, The Prevention and Elimination of Fatigue in HIV, Ortho Biotech

1994

- Miami, FL, April, The Immune Power Comprehensive Healing Program for HIV, Mercy Hospital.
- Miami, FL, April, A Comprehensive Treatment Program for HIV - Is Success Possible?, People with AIDS Coalition.
- Oakland, CA, February, The Comprehensive Treatment Program for HIV, Annual Meeting for Hemophiliac Society of Northern California.

1993

- San Francisco, CA, December, New Trends in HIV Treatment, San Francisco General Hospital Department of Family Practice Grand Rounds.
- Key West, FL, December, The Immune Power Comprehensive Healing Program for HIV.
- Fort Lauderdale, FL, December, The Immune Power Comprehensive Healing Program for HIV, Broward County Library.
- Orlando, FL, December, New Trends in HIV Treatment, Until There is a Cure Conference.

Jon D. Kaiser, M.D.

Clinical Faculty
UCSF School of Medicine
San Francisco, CA

Biography:

Jon D. Kaiser, M.D. was born in New York City in 1959. After graduating from the State University of New York with a degree in Philosophy with a Specialization in Biochemistry, he attended medical school at the University of Texas Medical School in Houston. During his medical school training, he received honors in Internal Medicine and Emergency Medicine, but at the same time became disheartened at the purely mechanistic approach to the treatment of disease that he was being taught. It was during this time that Dr. Kaiser began to explore the fields of nutrition, natural therapies, and emotional healing techniques.

In 1984, Dr. Kaiser began postgraduate training in Internal Medicine at the Kaiser Foundation Hospital in San Francisco. It was at this time that he began treating patients who were infected with the HIV virus. Several years later, after gaining experience in emergency medicine and family practice, Dr. Kaiser opened his private practice which quickly grew to capacity because of the intelligent and comprehensive approach he brought to the treatment of HIV infection, Cancer, and other immune system disorders. In 1993, Dr. Kaiser published his first book, Immune Power: A Comprehensive Treatment Program for HIV (1993 St. Marin's Press) which was critically acclaimed as well as a best seller in the SF Bay Area.

In 1997, Dr. Kaiser became Medical Director of The Jon Kaiser Wellness Center providing primary care to over fifteen hundred seriously ill patients in San Francisco. In early 2000, Dr. Kaiser re-entered private practice as an Integrative Medicine Consultant, helping patients recover from complex medical conditions using a unique integration of natural and standard medical therapies. His second book, Healing HIV: How To Rebuild Your Immune System (1999 HealthFirst Press), updated his comprehensive treatment approach including new information on micronutrient therapy, hormonal support, as well as the latest research on antiviral therapy.

Dr. Kaiser has been treating patients with HIV and other immune system disorders for the past twenty years. He is a currently a member of the Clinical Faculty at the University of California, San Francisco Medical School.

Dr. Kaiser is well known for his nationwide lectures on optimizing HIV care and his audiences consistently rate his HIV Treatment Update programs as highly valuable to their care. His ultimate goal is to help patients and health care providers treat complex medical conditions utilizing an integration of natural and standard medical treatments.

JAIDS Journal of Acquired Immune Deficiency Syndromes
33:605–607 © 2003 Lippincott Williams & Wilkins, Inc., Philadelphia

Brief Report

Effect of Antioxidants on Glucose Metabolism and Plasma Lipids in HIV-Infected Subjects With Lipoatrophy

*†Grace McComsey, †Heather Southwell, †Barbara Gripshover, †Robert Salata, and †Hernan Valdez

**Rainbow Babies and Children's Hospital, and †Center for AIDS Research, Case Western Reserve University and University Hospitals of Cleveland, Ohio*

Summary: Ten HIV-infected nucleoside reverse transcriptase inhibitor–treated subjects with lipoatrophy or sustained hyperlactatemia were given antioxidants: vitamins C, E, and *N*-acetyl cysteine. After 24 weeks, anthropometrics did not change significantly, except for a modest decrease in the waist-to-hip ratio. Fasting low-density lipoprotein cholesterol trended toward lower values. Fasting glucose significantly increased along with a significant increase in homeostatic model assessment values, reflecting an increase in insulin resistance. Controlled trials are required to evaluate directly the effects of these agents on lipid and glucose metabolism. **Key Words:** metabolic, antioxidants, lipodystrophy, lipoatrophy, lipids

Lipoatrophy and hyperlactatemia are well-recognized complications of antiretroviral therapy that have been linked to nucleoside reverse transcriptase inhibitor (NRTI)-induced mitochondrial toxicity.[1–4] The exact mechanism of this mitochondrial dysfunction remains unclear, but several studies suggested a link to increased oxidative stress. Zidovudine has been shown to increase 8-oxo-7,8-dihydro 2-deoxyguanosine (8-oxo-dG), a marker of oxidative damage to DNA.[5] Antioxidants (vitamins C and E) resulted in significant decrease in 8-oxo-dG and prevented morphologic changes of muscle mitochondria in zidovudine-treated mice.[6] Similar changes in oxidative markers were seen with stavudine therapy, and these changes were also prevented by concomitant treatment with antioxidants.[7] One study in HIV-infected subjects showed that daily supplementation with vitamin E, 800 IU, and vitamin C, 1000 mg, did result in a significant decrease in lipid oxidative markers and produced a trend toward a reduction in viral load.[8]

Supported by a grant from the Campbell Foundation.

Address correspondence and reprint requests to Grace McComsey, Rainbow Babies and Children's Hospital, 11100 Euclid Ave- mail stop 8A, Cleveland, OH 44106. E-mail: mccomsey.grace@clevelandactu.org

Manuscript received March 3, 2003; accepted May 28, 2003.

We conducted this pilot trial of antioxidants to explore the possible contribution of oxidative stress to lipoatrophy or sustained hyperlactatemia. The study was approved by the Institutional Review Board of the University Hospitals of Cleveland; all subjects gave written informed consent. HIV-infected subjects from the University Hospitals of Cleveland John T. Carey Special Immunology Unit were approached to participate if they had either lipoatrophy or sustained hyperlactatemia and were receiving stable NRTI-containing therapy for at least 12 months. Lipoatrophy was defined as patients' self-report of decrease in fat in at least 2 of the following areas: face, arms, legs, or buttocks. This had to be confirmed by the investigator and by an experienced registered dietician. Sustained hyperlactatemia was defined as reproducible elevated lactate levels of >2× the upper limit of normal (>4.8 m*M*). Fasting venous lactate levels were collected following ACTG guidelines, without the use of tourniquet, fist clenching, and with immediate processing by the local laboratory.[9] No specific dietary advice was provided to the subjects. Patients were continued on their current antiretrovirals while antioxidants were added. The primary study end point was a change in peripheral fat, as assessed by the subject, the clinician, and by anthropometric measurements. Changes in CD4,

EXHIBIT 2

HIV-1 RNA, and metabolic indices were assessed at weeks 0, 4, 8, 16, and 24. In addition, a registered dietician performed serial anthropometrics and bioelectrical impedance measurements of fat and lean body mass. Differences between baseline and on-treatment values were analyzed using Student t test; a 2-sided $P < 0.05$ was considered significant.

Ten subjects (2 women) aged 43 years (range 35–50) were enrolled into this pilot trial. All subjects were judged to be adherent to their antiretroviral regimen. Nine subjects had lipoatrophy at baseline. The only subject enrolled with no lipoatrophy had sustained hyperlactatemia for 4 months prior to study entry.

All subjects received open label treatment with vitamin E at 800 IU/d, vitamin C at 1000 mg/d, and *N*-acetyl cysteine (NAC) at 600 mg twice daily. The NAC was compounded into a capsule formulation by a local registered pharmacist, because only a foul-smelling liquid formulation is available in the United States. All subjects were receiving a stable NRTI-containing regimen for a median duration of 34 ± 16 months prior to study entry. The NRTIs at study entry were stavudine/lamivudine (4), zidovudine/lamivudine (3), didanosine/stavudine (1), didanosine/lamivudine (1), and abacavir/lamivudine (1). Eight were also receiving 1-2 protease inhibitor(s); the other 2 were receiving efavirenz. The duration of antiretroviral therapy prior to study entry was 76 ± 34 months. Baseline CD4 was 627 ± 316 cells/mm^3. Nine subjects had HIV-1 RNA of <400 copies/mL at study entry.

Table 1 summarizes the baseline data and the changes after 24 weeks of study drugs. Lactate levels were normal in the 9 subjects with lipoatrophy. In the 1 subject with sustained asymptomatic hyperlactatemia, lactate was 4.92 at study entry. All subjects tolerated study drugs without adverse events. One subject was lost to follow-up at week 8 and therefore was excluded from the analysis. The 1 subject with hyperlactatemia decided to enroll in a structured treatment interruption study and discontinued his antiretrovirals at week 20. His lactate was 3.73 at week 16 and 1.3 at week 24. Because of the on-study discontinuation of antiretrovirals as well as the lack of lipoatrophy, he was excluded from the final analysis.

Neither clinician, registered dietician, nor patients noticed any improvement of the study subjects' peripheral fat. There was no modification of exercise, diet, lipid-lowering drugs, or insulin-sensitizing agents throughout the study period. Fasting (≥12 hours) triglycerides and total and high-density lipoprotein cholesterol levels did not change significantly. Fasting low-density lipoprotein cholesterol (calculated) trended down from 124 ± 48 mg/dL at baseline to 102 ± 32 mg/dL at week 24 (P = 0.06).

TABLE 1. *Baseline characteristics and changes after 24 weeks of N-acetyl cysteine and vitamins E and C*

Index (mean ± SD)	Study entry n = 10	Week 24 n = 8	P value
Lactate (mM)	1.6 ± 1.3	1.7 ± 0.5	0.21
Total cholesterol (mg/dL)	220 ± 55	193 ± 41	0.89
LDL cholesterol (mg/dL)	124 ± 48	102 ± 32	0.06
HDL cholesterol (mg/dL)	43 ± 18	40 ± 8	0.62
Triglycerides (mg/dL)	264 ± 185	253 ± 120	0.78
Glucose (mg/dL)	84 ± 11	110 ± 21	0.017
Insulin (IU/mL)	14.2 ± 15.8	54 ± 76	0.1
HOMA	2.75 ± 2.69	7.20 ± 5.77	0.03
C peptide (ng/mL)	3.7 ± 2.4	7.7 ± 6	0.093
Weight (kg)	80 ± 5	81 ± 8	0.55
Fat (%)	23 ± 13	23 ± 13	0.9
Fat (lb)	41 ± 26	43 ± 29	0.88
Lean body mass (%)	38 ± 7	38 ± 7	0.89
Lean body mass (lb)	66 ± 10	66 ± 11	0.78
Waist-to-hip ratio	0.94 ± 0.06	0.92 ± 0.05	0.05
Mid-arm circumference (cm)	32 ± 3	32 ± 3	0.76
Biceps skinfold (mm)	12 ± 15	12 ± 13	0.83
Triceps skinfold (mm)	16 ± 16	14 ± 16	0.42
Midthigh circumference (cm)	51 ± 5	48 ± 5	0.14
Thigh skinfold (mm)	16 ± 16	15 ± 14	0.67
Midcalf circumference (mm)	37 ± 2	38 ± 3	0.27
Abdomen skinfold (mm)	18 ± 14	18 ± 11	0.89
CD4$^+$ cell count (cells/mm^3)	627 ± 316	605 ± 460	0.49
HIV-1 RNA <400 copies/mL	9/10	8/8	0.8

LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA, homeostatic model assessment.

Standardized anthropometrics revealed no change in circumferences or skinfold thickness; waist-to-hip ratio decreased from 0.94 ± 0.06 at baseline to 0.92 ± 0.05 at week 24 (P = 0.05). Fasting glucose increased significantly from a median of 84 ± 11 mg/dL at baseline to 110 ± 21 mg/dL at week 24 (P = 0.017). Fasting insulin trended upward from 14.2 ± 15.8 IU/mL at baseline to 54 ± 76 IU/mL at week 24 (P = 0.1). Homeostatic model assessment of insulin resistance (HOMA-IR), a widely used index of insulin sensitivity, significantly increased from 2.75 ± 2.69 at study entry to 7.20 ± 5.77 at week 24 (P = 0.03). Similarly, C peptide trended upward from 3.7 ± 2.4 ng/mL at baseline to 7.7 ± 6 ng/mL at week 24 (P = 0.093). Serum lactate and transaminases remained unchanged.

Lipoatrophy is a distressing long-term complication associated with decreased quality of life and disincentive for adherence to antiretrovirals.[10,11] To date several strategies have been unsuccessful in reversing this condition; a partially successful one has been the replacement of stavudine with abacavir.[12–14] However, subjects may experience lipoatrophy while on abacavir, or in some instances, this strategy may not be suitable because of prior antiretroviral experience. This suggests the need to in-

vestigate strategies that do not require switches in antiretroviral therapy.

There is a rationale for testing of antioxidants in lipoatrophy and hyperlactatemia. The choice of the dose and type of antioxidants for this study was based on studies showing success in preventing NRTI-induced mitochondrial toxicity[6,7] and in decreasing lipid oxidation markers.[8] The antioxidants used in this pilot trial were well tolerated, except for an increase in fasting glucose and in HOMA-IR, a widely used index of insulin resistance, which accounts for both fasting insulin and glucose levels and is known to correlate well with clamp techniques. These findings are of concern and suggest increasing insulin resistance. Alternatively, this could represent the natural history of insulin resistance in lipoatrophy. Favorable trends toward lower low-density lipoprotein cholesterol and waist-to-hip ratios are encouraging. We acknowledge the limitations of this study, mainly the small sample size and the lack of sensitive fat imaging, such as CT scan or MRI. Therefore this study was unable to detect small changes in peripheral fat. Controlled studies are required to evaluate directly the effects of these agents on lipid and glucose metabolism.

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